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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,203	ESPY ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6|100
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 9/22/2003. Claims 1-36 have been canceled, and claims 37-79 have been added. Claims 37-79 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

THE FOLLOWING ARE NEW REJECTIONS NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 37-50 and 68-75 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al.(J. gen. Virol. 1986) in view of Rose et al.(US Patent 5,925,733) and in further view of Wittwer et al.(US Patent 6,174,670).

Davison et al. teach the complete DNA sequence of Varicella-Zoster virus including genes 28 and 29 and SEQ ID NOS: 1-8. Through their analysis of the sequence, the reference teaches a genome containing 70 genes distributed about equally between the two DNA strands.

The discerned organization of VZV genes and that deduced for herpes simplex virus type 1 (HSV-1) from published transcript mapping data indicate that these two members of the *Alphaherpesvirinae* are very similar in gene layout(Summary). Comparisons of the predicted amino acid sequences of VZV proteins with those available for HSV-1 proteins generally suggest evolution from an ancestral genome, and allow the functions of several VZV genes to be deduced. The reference also teaches the usefulness of comparisons between VZV and HSV-1, as these viruses possess several conserved genes arranged collinearly in the genomes. The hypothesis resulting from this finding is that the two genomes have similar gene arrangements and was confirmed by the reference's comparison of the VZV gene layout deduced from the DNA sequence with that of HSV-1 proposed from currently available transcript mapping and sequence data. Consequently, the functions of several VZV genes can be identified on the basis of our knowledge of the molecular genetics of HSV-1, which far exceeds that of any other herpesvirus(Pg. 1760). The reference further specifically teaches properties of the proteins coded by predicted VZV genes 28 and 29 as DNA polymerase and Major DNA-binding proteins respectively(Table 1), the reference further teaches the position of each gene's start and stop codons and their molecular weights. The reference's sequence provides a firm foundation on which to build a detailed understanding of VZV infection at the molecular level. This knowledge may be applied in the development of effective treatments for the diseases caused by this virus. The sequence has also given the first complete view of the gene layout in the *Alphaherpesvirinae,* and has allowed our knowledge of the proposed functions of VZV genes to increase from almost nothing to equal that of HSV-1.

Davison et al. do not teach their varicella-zoster genomic sequence in the form of specific gene 28 primers and probes used in a FRET based PCR detection method, nor do they teach the subtleties of the PCR reaction embodied by claims 45-48, 50, 68-75 and 79.

However, Rose et al. teach the specific gene 28 primers and probes used in a PCR based detection assay using fluorescently-labeled probes(Col. 40), and further that altering the number of amplification cycles to obtain the desired fragment as being a routine matter for a practioner of ordinary skill in the art(Col. 32) The reference thus teaches the detection of VZV through the use of oligonucleotides, shown in their table 4, that are generally useful for hybridizing with DNA polymerase encoding polynucleotide segments(UL30, gene 28) isolated from biological samples such as blood, spinal fluid, and other liquid samples of biologic origin(Col. 23). The reference teaches that this may be conducted to detect the presence of the polynucleotide, or to prime an amplification reaction so that the polynucleotide may be characterized further. Rose et al. teach that suitable targets include polynucleotides encoding a region of a DNA polymerase from a wide spectrum of herpes viruses, including human varicella-zoster(Table 1 and Col. 31). The reference further teaches making these primers specific to UL30, a DNA Polymerase(aka gene 28 and SEQ ID NOS:1-4) and using them in an amplification reaction to hybridize to the target DNA and thereby act as a primer for the polymerization reaction(Col.32). The reference further teaches the use of 2 additional oligonucleotides as probes in a detection assay(Col. 34). The reference thus teaches using SEQ ID NOS 1-4 in the context of detecting Varicella-Zoster virus in a PCR based method. Lastly, the kits of this method teach control samples, the reagent that renders the procedure specific: a reagent polynucleotide, used for detecting target DNA as well as means of detection(Col. 53).

Rose et al does not exemplify the exact PCR method steps used in the present invention's FRET-based assay.

However, Wittwer et al. (US Patent 6,174,670) teach a method of PCR amplification for the detection of viral polynucleotides, specifically for the PCR-amplified products of hepatitis B virus(See for example, FIG 37-39 and 41A&B), but the reference teaches a general method applicable to detection of any virus. The reference teaches a method for detecting the presence or absence of any virus and exemplifies amplification of Hepatitis B in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a hybridizing step, wherein said amplifying step comprises amplifying a portion of a viral nucleic acid molecule from said biological sample using a pair of viral specific primers, thereby producing an amplification product specific to the hepatitis virus, wherein said hybridizing step comprises hybridizing a pair of probes to said amplification product, wherein the members of said pair of probes hybridize within no more than five nucleotides of each other, wherein a first probe of said pair of probes is labeled with a donor fluorescent moiety(fluorescein, Col. 4) and said second probe of said pair of probes is labeled with a corresponding acceptor fluorescent moiety(Cy5TM or Cy5.5TM Col. 4);(See Abstract, Brief Summary of Invention) and Fig. 18 for example) and

detecting the presence or absence of fluorescence resonance energy transfer(FRET) between said donor fluorescent moiety of said first probe and said acceptor fluorescent moiety of said second probe upon hybridization of said pair of probes to said amplification product, following excitation of the biological sample at a wavelength absorbed by said donor fluorescent

moiety and visualizing and/or measuring the wavelength emitted by said acceptor fluorescent moiety, after each cycling step, all in real time(Col.5 and Col.19 for example).

wherein the presence of FRET is indicative of the presence of the hepatitis virus in said biological sample, and wherein the absence of FRET is indicative of the absence of hepatitis virus in said biological sample and further wherein the melting temperature of the amplification product confirms said presence or said absence of said virus being tested(Col 7, for example). Wittwer et al. further teaches the above method comprising preventing amplification of a contaminant nucleic acid(DETX 163 and 143 and 148 for example), and furthermore in claims 73-78 the use of a selected control template and corresponding primers and probes with which it may be detected. Lastly, Wittwer et al teach the above method wherein the presence of said FRET within 50, 40, and 30 steps is indicative of the presence of a hepatitis infection, or generally a viral infection in said individual(See for example Fig.20-27 and corresponding text).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to detect the sequences of Davison et al. through the PCR method of Rose et al in view of Wittwer et al. The prospect of detecting an infectious varicella-zoster virus polynucleotide sequence in light of the teachings of the conserved nature of the DNA polymerase encoding sequences of all herpes virus, would provide the motivation necessary to practice the combined teachings of Davison and Rose and detect gene 28(DNA polymerase encoding) and specifically taught SEQ ID NOS:1-4, in a PCR-based method with specific primers and probes taught for gene 28 by the sequences of both Davison and Rose(SEQ ID NOS:1-8 and 1-4 respectively). Furthermore, Wittwer's teachings of a FRET based PCR method used to detect viral components, would have been further obvious to incorporate into the teachings of Davison

and Rose, as current methods of PCR carry out temperature cycling slowly and empirically and additional time consuming steps are required. Thus, this method of Wittwer provides a great advance in the art for monitoring hybridization during PCR and analyzing the reaction while it is taking place, that is, during or immediately after temperature cycling without manipulation of the sample(Col.3). The reference concludes that by monitoring hybridization during PCR, the underlying principles that allow PCR to work can be followed and used to analyze and optimize a PCR reaction during amplification. As a whole then, the combined teachings of Davison, Rose and Wittwer provide a more accurate method for the early detection of a VZV infection at the molecular level(Davison, Pg. 1813).

2. Claims 37-75(51-67 newly rejected) and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al.(J. gen. Virol. 1986) in view of Rose et al.(US Patent 5,925,733), in further view of Wittwer et al.(US Patent 6,174,670) and in even further view of Beards et al. (Journal Medical Virol. 1998).

In view of the combined teachings of a FRET-based PCR method of detecting VZV of Davison, Rose, and Wittwer stated above, these references do not teach gene 29 specific primers and probes with which to practice the method.

However, Beards et al. teach 4 sets of specific primers for gene 29 and VZV detection(156). It should be further noted that the reference's teaching of a nested primer, PCR system including 4 different sets of primer pairs, provides a motivation for using the nested primers alternatively as probes for the expected benefit of providing a more specific PCR product.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have supplemented the teachings of Davison(SEQ ID NOS: 1-8 inherent in genome), Rose, and Wittwer with the primers/probes specific for gene 29(SEQ ID NOS: 5-8) of the VZV for the expected benefit of obtaining a more accurate diagnostic method for the presence of the virus.

3. Claims 76-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al(J. gen. Virol, 1986) in view of Rose et al.(US Patent 5,925,733) and Wittwer et al.(US Patent 6,174,670) and in further view of Longo et al.

In view of the combined teachings of a FRET-based PCR method of detecting VZV of Davison, Rose, and Wittwer stated above, these references do not teach however the steps of claims 76-78 involving preventing amplification of a contaminant nucleic acid.

However, Longo et al. teach the step of preventing amplification of a contaminant nucleic acid comprising performing said amplifying step in the presence of uracil and through the further treatment of the biological sample with uracil-DNA glycosylase prior to a first amplifying step(Summary). Longo et al teach that carry-over contamination of new PCRs by the abundant amplification products can be a significant problem, due to the abundance of PCR products, and to the ideal structure of the contaminant material for re-amplification.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to add the steps of Longo et al in order to have prohibited these chances of contamination and thereby the chance of obtaining false positives.

4. Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al.(J. gen. Virol. 1986) in view of Rose et al.(US Patent 5,925,733) in further view of Wittwer et al.(US Patent 6,174,670) and in an even further view of Sauerbrei et al.(Journal of Clinical Virology, 1999).

In view of the combined teachings of a FRET-based PCR method of detecting VZV of Davison, Rose, and Wittwer stated above, these references do not teach however the step wherein the biological sample is selected from the group consisting of dermal swabs, cerebrospinal fluid, ganglionic tissue, brain tissue, ocular fluid, blood, sputum, bronchio-alveolar lavage, bronchial aspirates, lung tissue, and urine of claim 79.

However, Sauerbrei et al. teach virological diagnosis of Zoster in vesicle fluid and swabs from the dermatomes of the chest, head, neck, waist, and pelvis in addition to serum sample(32). The reference teaches a study of biological samples of 100 patients with Zoster being analyzed by detecting DNA using PCR. The findings were compared with those obtained by traditional virological and serological methods. Primers and probes specific for VZV gene 28 and 29 were used for amplification and detection of the VZV DNA by PCR(Table 1). The results of this study show that PCR detects VZV in Zoster with a high rate of sensitivity and specificity. PCR results were available within 1 day and showed no cross-reaction to HSV. The reference therefore teaches that PCR with primers of genes 28 and 29 is the method of choice for rapid diagnosis of Zoster. Primers for genes 28 and 29 are both necessary to detect the maximum number of cases, as taught by the reference's Table 2. The reference further teaches the use of positive and negative controls and furthermore "there were no cross-reactions to VZV with any

of the oligonucleotides used (specificity 100%)"(34) in their provision for preventing amplification of a contaminant nucleic acid.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to have practiced the FRET-based viral detection method of Wittwer using PCR with primers of genes 28 and 29 as the method of choice for rapid diagnosis of Zoster since the genomic sequence of Zoster and therefore SEQ ID NOS: 1-8 are taught by Davis and said detection of biological samples such as from blood, spinal fluid, and other liquid samples of biologic origin is taught by Rose and furthermore since such similar primers for genes 28 and 29 are taught by Sauerbrei et al. to incorporate additional biological samples taught by Sauerbrei et al. for the expected benefit of detecting the maximum number of Varicella-Zoster cases. As a whole then, the combined teachings of Davis, Wittwer, Rose and Sauerbrei et al provide a more accurate and encompassing method for the early detection of a VZV infection.

5. Response to Arguments:

Although the examiner acknowledges applicants' arguments concerning their newly added claims, ie. applicants' assertion that they recite a "particular primer or probe sequence" and thus are not alone or in combination with the cited art, obvious to one of skill in the art, is not found to be convincing. The claims are not directed to, or limited to a particular primer or probe sequence. Furthermore, applicants have not shown any unexpected results associated with primers/probes comprising or consisting of the recited sequences. In the absence of evidence to the contrary, all primers and probes to each of genes 28 and 29 are considered to be equivalents and the above combined teachings of the prior art would have lead one of ordinary skill in the art to the claimed primer and probe sequences. Applicants' assertion that the "Davison et al.

reference does not teach or suggest using the particular primers and probes recited in the pending claims in the methods to detect the presence or absence of VZV" is noted however, the examiner maintains that "particular primers and probes" are not being claimed. The many sequences that "comprise" primers and probes are being claimed and therefore are obvious in light of such teachings as the entire genome of Davison et al. The same is true for the Rose et al. reference and that of Beards et al.. The examiner maintains that the art cited, effectively makes obvious the invention as broadly as it is currently claimed and without a showing of unexpected results associated with the primers and probes.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

12/18/2003

CARLA J. MYERS
PRIMARY EXAMINER